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Prospective memory deficits in subjects with schizophrenia spectrum disorders: A comparison study with schizophrenic subjects, psychometrically defined schizotypal subjects, and healthy controls

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Abstract

Memory impairment is one of the core deficits in schizophrenia. This study explored the memory profiles of schizophrenic and psychometrically defined schizotypal subjects. The study participants included 15 patients with schizophrenia, 41 schizotypal subjects, and 20 healthy controls. All of the participants completed verbal and visual memory, working memory, and prospective memory tasks. The results showed that patients with schizophrenia were impaired in all aspects of memory function, whereas the schizotypal subjects tended to show moderate to large impairment effect sizes in prospective memory. It is suggested that prospective memory be considered a potential endophenotype of schizophrenia.

Keywords: Memory; Prospective memory; Schizophrenia; Schizotypal; Endophenotype

1. Introduction

Schizophrenia is a heritable disorder (Kendler and Diehl, 1993), but traditional linkage and association studies produce inconsistent findings regarding the susceptibility loci (Tsuang and Owen, 2002). Thus, in recent years researchers have adopted the endophenotype approach to study the gene basis of schizophrenia (Gottesman and Gould, 2003; Gould and Gottesman, 2006). Endophenotypes are more proximal functions of gene action than the diagnosis of schizophrenia itself, and hence it should be simpler to localize the genetic loci of endophenotypes than to localize those for schizophrenia (Gottesman and Gould, 2003; see Gur et al., 2007 for a review). There are different kinds of endophenotypes, and cognitive endophenotypes have been extensively studied.

Cognitive dysfunction has been identified as one of the central abnormalities that is found in schizophrenic patients (Roitman et al., 2000), and memory impairment is one of the core deficits in schizophrenia (Loughland et al., 2007;

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Saykin et al., 1994; Weiss and Heckers, 2001). Patients with schizophrenia have been found to be impaired in verbal memory (Cirillo and Seidman, 2003; Joyce, 2005; Wittorf et al., 2004), verbal working memory (Conklin et al., 2000, 2005), visuospatial working memory (Lencz et al., 2003; Goldberg et al., 2003) and prospective memory (Elvevag et al., 2003; Shum et al., 2004; Kumar et al., 2005; Woods et al., 2007). Most studies have found that cognitive dysfunction is correlated with negative symptoms (e.g., O'Leary et al., 2000; Chan et al., 2006a,b).

In addition to patients with schizophrenia, the schizophrenia spectrum population includes clinically defined schizotypal personality disorder (SPD) subjects, relatives of schizophrenic patients, psychosis-prone subjects (those who score high on psychometric tests for schizotypy) and schizoaffective disorder (Cadenhead et al., 1999). These populations may demonstrate cognitive impairment and are more likely to develop schizophrenia in comparison to the general population.

In particular, researchers have found impairments in the verbal memory and working memory of clinically identified SPD subjects (Cadenhead et al., 1999; Mitropoulou et al., 2002, 2005; Roitman et al., 2000; Voglmaier et al., 1997, 2000; Siever et al., 2002; Smith et al., 2006) and unaffected biological relatives of schizophrenic patients (Cannon et al., 1994; Conklin et al., 2000, 2005; Lyons et al., 1995; Toomey et al., 1998; Keri et al., 2001; Whyte et al., 2005; Wittorf et al., 2004). Psychometric schizotypes have also been found to have impaired spatial working memory (Gooding and Tallent, 2003; Park et al., 1995; Park and McTigue, 1997; Tallent and Gooding, 1999).

Gur et al. (2007) reviewed the literature in schizophrenia on verbal memory and working memory, and found they fulfilled the criteria of endophenotype (i.e., association with illness; state independent; heritable; found in unaffected relatives at a higher rate than in the general population, in addition to at least partially known neurobiological substrate) and suggested that verbal memory and working memory are endophenotypes for schizophrenia.

However, previous studies have mainly focused on retrospective memory, and the prospective function of memory has not yet been fully studied. Prospective memory (PM) refers to remembering to perform an intended action in the future. This kind of memory is important in daily living, for example, remembering to turn up for a doctor's appointment, or remembering to make a telephone call at the right time are examples of activities that require the good working of prospective memory. Also, failure in prospective memory (forgetting to take medication on time, forgetting to turn off an electrical appliance) may lead to undesirable consequences (Shum et al., 2001). PM is classified as event based (remembering to perform an action when a particular event occurs in the environment), time based (remembering to perform an action at a certain time or after a period of time), or activity-based (remembering to do something after finishing a certain activity) (Einstein and McDaniel, 1990; Kvavilashvili and Ellis, 1996).

Research indicates that prospective memory is related to frontal lobe function, and includes studies of frontal lesion patients (Burgess et al., 2000; Daum and Mayes, 2000) and neuroimaging studies (Okuda et al., 1998, 2006; Burgess et al., 2001, 2003; den Ouden et al., 2005; Simons et al., 2006). Neuroimaging studies have found that the lateral prefrontal cortex and rostral frontal cortex (BA 10) especially are activated when subjects perform PM tasks, and that the activations cannot be attributed to task difficulty. Schizophrenic patients have showed impairment of frontal lobe functioning, especially in the dorsal lateral prefrontal cortex (DLPFC), whether they were chronic or first episodic (Callicott et al., 2000; Goldman-Rakic, 1999; Ritter et al., 2004; Curtis et al., 1998; Fu et al., 2005).

There are few studies of PM in schizophrenic patients. In a study by Elvevag et al. (2003) that assessed habitual PM in patients with schizophrenia, participants were asked to play a game and do a PM task once per trial. Participants had to repeat the game 10 times. The results showed that patients made more omission errors (did not do the PM task) than did the healthy controls. Shum et al. (2004) found chronic schizophrenic patients performed worse in all event, time-, and activity-based PM tasks, and did especially worse in time-based tasks; patients also showed time monitoring deficits and performed worse in all frontal lobe tasks (Design Fluency Test (DFT), Tower of London test, and Wisconsin card sorting test). Kumar et al. (2005) found that even drug-free or drug-naïve schizophrenic patients showed impairment in event-based PM. The impairment could not be attributed to motivation or memory of instructions, and their PM performance did not correlate with any clinical symptoms. Woods et al. (2007) also found schizophrenic patients showed impairments in both event and time-based PM, and mainly the cue detection and self-initiated retrieval components of PM were impaired.

Taken together, these studies indicate a PM deficit can be found in schizophrenic patients and that this deficit is relatively stable. We explore the PM deficits in schizophrenia by using semantic and perceptual materials as ongoing tasks and suggest that PM is a general deficit in schizophrenia, independent of materials used. Also, we suggest that the psychometrically defined schizotypal participants will perform worse than the healthy controls.

This study aimed to further examine memory performance, and particularly, prospective memory performance in schizophrenia. It was hypothesized that memory performance will follow this pattern: healthy control better than schizotypal subject better than schizophrenic subject. It was also hypothesized that memory performance will be correlated with clinical manifestations, especially the negative symptoms in patients with schizophrenia.

2. Method

2.1. Participants

Fifteen schizophrenic subjects who fulfilled the diagnostic criteria of DSM-IV (American Psychiatric Association, 1994) based on diagnostic interviewing that used the Structured Clinical Interview for DSM-IV and medical record reviews were recruited from the Institute of Mental Health, Peking University; people with a history of neurological illness or alcohol/drug dependence (according to clinical records, information from clinician and interview with the patients) were excluded. The 15 subjects included 10 paranoid and 3 undifferentiated patients and 2 unspecified patients. Clinical symptoms were rated using the Positive and Negative Symptom Scale (PANSS, Kay et al., 1987). All of the patients were being treated with atypical antipsychotics. Medication side effects were assessed with the Abnormal Involuntary Movement Scale (AIMS, Smith et al., 1979) and Barnes Akathisia Rating Scale (BARS, Barnes, 1989).

Four hundred and thirty-five college students were recruited from Peking University, Sun Yat-Sen University, Guangdong Vocational College of Mechanical and Electrical Technology, and Zhongkai University of Agriculture and Technology. They were screened by the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991, adapted Chinese version, Chan et al., submitted for publication). According to the scoring criteria suggested by Raine (1991), people at the top fifteen percentile of the distribution scores were considered as schizotypal. Forty-three psychometrically defined schizotypal participants were initially identified (with a cut-off of 35). However, two of them showed no interest for further testing, so the final sample consisted of 41 schizotypal subjects. Research utilizing high schizotypal could overcome some of the confounds involved in studying actively symptomatic patients. These individuals are nonpsychotic, unmedicated (with antipsychotics) and unhospitalized. Moreover, study of this subgroup may provide important information on the possible cognitive underpinnings of psychotic symptoms.

Twenty healthy controls were also recruited from Peking University and Sun Yat-Sen University. They were screened by the SPQ (with the low fifteen percentile of the distribution scores) and also by a semi-structured interview conducted by a trained research assistant. None of the schizotypal subjects or healthy controls had any family history of psychiatric illness, or suffered from a neurological illness or alcohol/drug dependence.

Intellectual functioning was estimated by the short form (information, arithmetic, similarity, and digit span) of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Gong, 1992). This method of prorating has been used in estimating the intellectual functioning in schizophrenia (Blyler et al., 2000; Chan et al., 2005). Handedness was assessed by the Annett Handedness Scale (Spreen and Strauss, 1991). The demographic variables of the participants are shown in Table 1. The present study was approved by the ethics committees of all the corresponding institutes. Written informed consent was obtained from each of the study participants.

2.2. Measures

2.2.1. Prospective memory tasks

Event- and time-based prospective memory tasks were presented on a computer and were based on the paradigm of Einstein and McDaniel (1990). Ongoing tasks were divided into semantic and perceptual tasks. In the semantic event-based PM (se_ev) task, a four-character word was presented in the center of the screen and the participants were asked to judge whether the words were idioms or not. They were asked to press the "J" key to answer affirmatively and to press the "F" key to answer negatively (this was defined as the ongoing task); if there was an animal name in the word (e.g., horse), they were asked to press the spacebar (this was defined as the PM task). A total of 5 animal names appeared during the session and the time interval between the appearances of each name was approximately 1 min. These are horse, tiger, mouse, cock, and fish. The other words, as distractors, were obviously not animal names, such as sky, ground, long, color etc. The ongoing task words were selected from high frequency words (Zhang, 2005), and they were defined as idioms if they could be found in an idiom dictionary (Committee of Idiom Dictionary, 2004).

Table 1
Group demographics

	Schizophrenia (N=15)	Schizotypal (N=41)	Control (N=20)	
	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Male: female	13:2	34:7	9:11	0.003
Handedness (Right handed percentage)	93	95	100	0.547
Age (years)	28.73 (8.29)	20.07 (1.08)	22.70 (4.88)	0.001
Education (years)	13.53 (2.88)	13.80 (0.64)	14.90 (2.55)	0.057
IQ	97.00 (14.98)	94.00 (15.89)	121.95 (17.38)	0.001
Duration of illness (months)	82.33 (77.02)	–	–	
Medication (chlorpromazine equivalence mg/day)	245.29	–	–	
Medication side effect				
Abnormal Involuntary Movement Scale	1.07 (0.96)	–	–	
Barnes Akathisia Rating Scale	1.00 (0.85)	–	–	
PANSS				
Positive symptoms	17.93 (5.50)	–	–	
Negative symptoms	17.86 (5.46)	–	–	
General psychopathology	30.73 (7.58)	–	–	
Total score	66.53 (15.39)	–	–	
Schizotypal Personality Questionnaire				
Cognitive–perceptual		14.71 (3.38)	6.73 (3.78)	0.0005
Interpersonal		18.46 (4.47)	6.73 (4.06)	0.0005
Disorganized		10.93 (2.68)	4.60 (2.80)	0.0005
Total score		44.10 (5.87)	18.07 (8.37)	0.0005

Each word had a font size of 50, was white against a black background, appeared for 1500 ms, and was followed by a black screen for a time period, which varied randomly, of 1500 ms, 2000 ms, or 2500 ms. The numbers of trials were 88 for ongoing task trials and 5 for PM task trials, and there were several trials before the first PM trial and after the last PM trial. The participants were told that the two tasks (the ongoing task and the PM task) were of the same importance. At the end of the session, the sentence "Thank you for your participation! Bye" appeared on the screen. The participants were asked to press the "Enter" key upon seeing this sentence. PM performance was the rate of remembering to press the spacebar. The instruction present to the participants in this session was as follows: "There would be four-character word presented on the screen, please judge if it is a Chinese idiom or not. If it is an idiom, please press 'J' on the keyboard; and if it is not an idiom, press 'F'. And sometimes, there would be an animal name in the word, e.g., monkey, in this case, press the spacebar no matter whether the word is an idiom or not, you need not press 'J' or 'F' in this situation. This task is as important as the previous idiom judgment task. At the end of this task, the screen would present 'Thank you for your participation! Bye!', please press 'Enter' to finish the program."

The semantic time-based PM (se_ti) tasks were the same as the semantic event-based PM tasks except that a separate clock was put at the upper right part of the keyboard (the participants can see the time clearly without much physical movement of the head in case they refuse to see the clock if it requires much movement that would result inappropriateness), and the participants were asked to monitor the time throughout the experimental session. Each time the clock reached the minute (e.g., 12:23:00, the last two digits are 00), they were asked to press the spacebar. Also, there were no animal names attached to this task. There were 90 trials in this session.

In the perceptual event-based PM (pe_ev) task, a vague digit appeared in the center of the screen and the participants were asked to judge whether or not the digit was 0. The participants were asked to press the "J" key if the digit was 0 and to press the "F" key if the digit was not 0 (i.e., 2, 4, 6, or 8) (see Fig. 1(a), (b)). This was defined as the ongoing task. Sometimes the digit was regular (Fig. 1(a)) and sometimes it was irregular (Fig. 1(b)). The digit was between two bars, one above and one below it. If there was a down arrow under the vague digit, the participants were asked to press the spacebar whether the digit was 0 or not (see Fig. 1(c)). Five down arrows appeared during the session, and the interval between the appearances of each digit was approximately 1 min. The digit appeared on the screen for 300 ms, and following the appearance of the digit a black screen appeared for a time period, which varied randomly, of 1500 ms, 2000 ms, or 2500 ms. The numbers of trials were 122 for ongoing task trials and 5 for PM task trials, and there

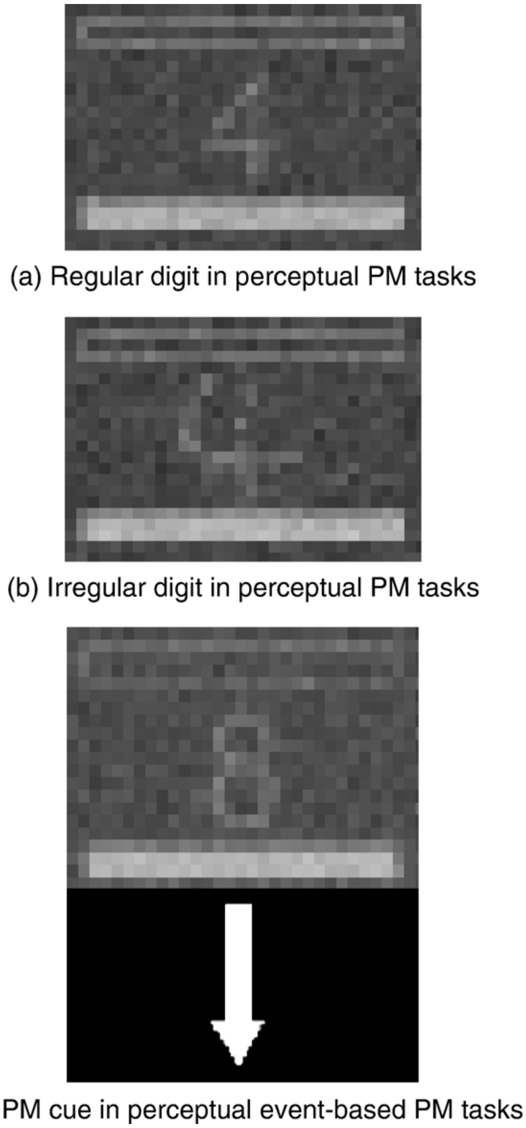

Fig. 1. Materials for perceptual PM tasks.

were several trials before the first PM trial and after the last PM trial. The participants were told that the two tasks (the ongoing task and the PM task) were of the same importance. At the end of the session, the sentence "Thank you for your participation! Bye" appeared on the screen. The participants were asked to press the "Enter" key upon seeing this sentence. PM performance was the rate of remembering to press the spacebar.

The perceptual time-based PM (pe_ti) tasks were the same as the perceptual event-based PM tasks except that a separate clock was put at the upper right part of the keyboard (the participants can see the time clearly without much physical movement of the head in case they refuse to see the clock if it requires much movement that would result inappropriateness), and the participants were asked to monitor the time throughout the experimental session. Each time the clock reached the minute (e.g., 12:23:00, the last two digits are 00), they were asked to press the spacebar. There were no down arrows in this task. There were 135 trials in this session.

Each of the above sessions lasted approximately 5 min. An activity-based PM task was defined as remembering to press the "Enter" key at the end of the above sessions when "Thank you for your participation! Bye" appeared on the screen. Each time that participants remembered to press the "Enter" key, they received a score of 1.

2.2.2. Working memory

Chinese Letter Number Span (Chan et al., in press) combinations, that is, digits (1 to 9) mixed with Chinese characters (in a specific sequence, such as A, B, C in English), were read to participants, and they were asked to rearrange the order so that digits came first, from small to big, and then the characters, in sequence.

The n-back (Callicott et al., 1998) task is a computerized measure of working memory. In this study, for the n-back task, there were four circles on the screen, and four digits (2, 4, 6, 8) appeared in the circles. The digits appeared in a fixed circle, one digit at a time. For the 0-back condition, participants were asked to press the digit they had just seen as quickly as possible; for the 1-back condition, participants were asked to press the digit just previous to the one they had seen; and for the 2-back condition, participants were asked to press the digit that they had seen two digits previously. Each digit appeared on the screen for 400 ms, and then disappeared for 950 ms, and in the next session, the digits appeared in a pre-fixed pseudo-random order.

2.2.3. Verbal and visual memory

The logical memory and visual reproduction measures from the Wechsler Memory Scale-Revised (Wechsler, 1987; Chinese version, Gong et al., 1989) were used to measure verbal memory and visual memory. For the logical memory task, the participant was told a short story and asked to recall it immediately and again 30 min later. For the visual reproduction task, the participant was shown two pictures (one at a time) for 10 s each, and asked to draw them immediately and again 30 min later.

2.3. Procedure

The participants were given a general introduction to the study, and the opportunity to ask questions following the introduction. Then, they signed an informed consent before testing began. IQ subscales were done between PM exercises and formal experiments. The four PM tasks were given in the following order: semantic time-based PM task, perceptual event-based PM task, semantic event-based PM task, and perceptual time-based PM task. Other tests were administered randomly. Finally, the participants were interviewed and patients' PANSS were rated.

2.4. Data analysis

Due to the significant differences in age, IQ, and education among groups, these variables were controlled for the analyses of PM, working memory, verbal memory, and visual memory using MANCOVA. For PM, ongoing task accuracy and reaction time were also analyzed. Effect sizes for group comparisons were calculated. For PM performance, all of the PM scores were transformed to a Z score and added together to generate a single index, and compared between groups. Since working memory is associated with PM performance (West et al., 2006), we controlled working memory as a covariate in the subsequent analyses. Correlation analysis was also done to see the relationship between schizotypal traits and cognitive performances in schizotypal participants, and between clinical variables and cognitive performance in schizophrenia patients.

3. Results

3.1. Schizophrenic patient vs. schizotypal subject vs. healthy control analysis

Significant differences were found in age [$F(2,73)=20.63$, $p<0.001$] and estimated IQ [$F(2,73)=21.08$, $p<0.001$], and a marginally significant difference was found in education [$F(2,73)=2.98$, $p<0.057$], so these variables were controlled in the subsequent analyses.

For PM performance, semantic event-based PM [$F(2,70)=8.03$, $p<0.001$] was significantly different among groups, post hoc tests revealed that schizophrenia patients performed poorer than controls ($p<0.001$) and schizotypal participants performed significantly poorer than patients ($p=0.002$); perceptual time-based PM [$F(2,70)=16.16$, $p<0.001$] was significantly different among groups, post hoc tests revealed that patients performed significantly poorer than controls ($p<0.001$), schizotypal subjects performed significantly poorer than patients ($p<0.001$); and semantic time-based PM [$F(2,70)=4.74$, $p<0.012$] was significantly different among three groups, post hoc tests revealed that patients performed poorer than schizotypal subjects ($p<0.005$), schizotypal subjects performed marginally significantly poorer than controls ($p=0.058$), schizotypal subjects performed marginally poorer than controls ($p=0.084$); perceptual event-based PM and activity-based PM were not significant and effect sizes were small to medium (Table 2).

All of the PM scores were transformed to a Z score and added together to generate a single index of PM function: Z_PM, which was significantly different between groups [$F(2,70)=11.71$, $p<0.001$], post hoc test found that patients performed significantly poorer than controls ($p<0.001$), patients performed marginally significantly poorer than schizotypal subjects ($p<0.001$).

When the working memory indicator Chinese Letter Number Span total correct was controlled to see the difference in PM among groups, the results indicated that semantic event-based PM, perceptual time-based PM, and semantic time-based PM still remained significant, the p values of which were 0.007 [$F(2,69)=5.35$], 0.001 [$F(2,69)=14.85$], and 0.011 [$F(2,69)=4.87$], respectively; Z_PM was also significant among groups, with $p<0.001$ [$F(2,69)=10.29$]. Post hoc tests found that for semantic event-based PM task, patients performed poorer than controls ($p=0.003$) and schizotypal subjects ($p=0.006$); for perceptual time-based PM task, patients performed poorer than controls ($p<0.001$) and schizotypal subjects ($p<0.001$); for semantic time-based PM task, patients performed poorer than schizotypal subjects ($p<0.01$) and schizotypal subjects performed marginally poorer than control ($p=0.084$); for Z_PM, patients performed poorer than controls ($p<0.001$) and schizotypal subjects ($p<0.001$).

For PM ongoing task accuracy, semantic event-based PM was significant [$F(2,70)=3.46$, $p<0.037$], while the others were not significant: F ranged from 0.30 to 1.40, and p ranged from 0.255 to 0.739. None of the PM ongoing task reaction time effects were significant: F ranged from 0.14 to 1.66, and p ranged from 0.197 to 0.871.

In working memory tasks, the Chinese Letter Number Span total correct [$F(2,70)=5.65$, $p<0.005$] and longest span passed [$F(2,70)=5.32$, $p<0.007$] reached significance. Post hoc tests showed that patients performed significantly poorer than controls ($p<0.001$) and schizotypal participants ($p<0.05$), whereas schizotypal participants performed marginally significantly poorer than controls ($p=0.084$) in Chinese Letter Number Span total correct responses. For the longest span passed, patients performed poorer than controls ($p<0.01$) and marginally poorer than schizotypal participants ($p=0.059$), whereas schizotypal participants performed marginally poorer than controls ($p=0.07$). No significant differences were found in n-back correct and reaction time. But a check on the effect sizes of performances revealed that there were medium to large effects demonstrated between schizophrenic patients

Table 2
Memory performance among groups

	Schizophrenia (N=15)		Schizotypal (N=41)		Control (N=20)				Cohen's d			
	M	SD	M	SD	M	SD	F	p	Sch vs HC	SPD vs HC	Sch vs SPD	Partial η^2
Prospective memory												
pe_ev	0.75	0.35	0.76	0.24	0.7	0.31	0.62	0.541	0.14	0.22	−0.05	0.017
se_ev	0.43	0.35	0.63	0.29	0.84	0.15	8.03	**0.001**	**−1.52**	**−0.91**	**−0.63**	**0.187**
pe_ti	0.39	0.37	0.81	0.3	0.99	0.04	16.16	**0.001**	**−2.27**	**−0.81**	**−1.25**	**0.316**
se_ti	0.45	0.42	0.7	0.39	0.85	0.31	4.74	**0.012**	**−1.08**	−0.43	**−0.60**	**0.119**
APM	2.67	1.72	3.29	1.27	3.35	1.23	1.62	0.206	−0.46	−0.05	−0.41	0.044
Z_PM	−2.80	3.92	0.23	2.25	1.63	2.12	11.71	**0.001**	**−1.56**	**−0.64**	**−0.95**	**0.251**
Working memory												
CLN_corr	10.67	2.41	13.44	3.24	18.2	4.46	5.65	**0.005**	**−2.10**	**−1.22**	**−0.97**	**0.139**
CLN_lg	4.53	1.06	5.39	1.05	6.9	1.37	5.32	**0.007**	**−1.93**	**−1.24**	**−0.82**	**0.132**
n-back_c	0.3	0.17	0.39	0.23	0.54	0.25	0.63	0.535	**−1.09**	**−0.61**	−0.44	0.018
n-back_rt	821.67	192.83	694.44	188.51	657	200.45	0.8	0.452	**0.84**	0.19	**0.67**	0.022
Verbal and visual memory												
LM_imme	8.27	4.74	12.24	3.93	13.2	3.61	3.76	**0.028**	**−1.17**	−0.25	**−0.91**	**0.097**
LM_delay	6.73	3.86	10.88	4.38	11.7	4.45	2.77	0.070	**−1.19**	−0.19	**−1.00**	**0.073**
VR_imme	22.47	1.81	23.15	1.49	23.6	0.88	0.64	0.530	**−0.79**	−0.37	−0.41	0.018
VR_delay	21.4	1.64	23	1.38	23.35	1.09	4.54	**0.014**	**−1.40**	−0.28	**−1.06**	**0.115**

pe_ev=perceptual event-based PM; se_ev=semantic event-based PM; pe_ti=perceptual time-based PM; se_ti=semantic time-based PM; APM=activity-based PM; Z_PM=sum of Z scores of PM performance; CLN_corr=Chinese Letter Number span total correct; CLN_lg=Chinese Letter Number span longest passed; n-back_c=n-back total correct; n-back_rt=n-back reaction time of correct responses; LM_imme=logical memory immediate recall; LM_delay=logical memory delayed recall; VR_imme=visual reproduction immediate recall; VR_delay=visual reproduction delayed recall; Sch=schizophrenia patients; SPD=schizotypal personality proneness; HC=healthy control. In p column, those less than 0.05 were in bold; in Cohen's d column, those larger than 0.5 (absolute value) were in bold, according to Cohen (1988), it's medium effect size; in partial η^2 column, those larger than 0.06 were in bold, according to Cohen (1988), it's medium effect size.

and healthy controls, and between schizophrenic patients versus schizotypal participants.

Significant difference was found in logical memory immediate recall [$F(2,70)=3.76$, $p<0.028$]. Post hoc analysis showed that patients with schizophrenia performed poorer than schizotypal participants ($p<0.01$) and controls ($p<0.05$) in immediate recall. Similar significant difference was found in visual reproduction delayed recall [$F(2,70)=4.54$, $p<0.014$]. Post hoc analysis showed that patients performed significantly poorer than controls ($p<0.05$) and schizotypal participants ($p<0.005$) in this domain. Although no significant differences were found in other test performances, medium to large effect sizes were demonstrated between the groups (see Table 2). Fig. 2 shows the prospective memory profiles of the three groups, and Fig. 3 shows the profiles for other memory measures. The score of the n-back reaction time was reversed for easy understanding, and a lower score indicates poorer performance (all scores in the figure were Z-transformed). From the figures it can be seen that the schizophrenic patients performed the worst in all memory tasks except for perceptual event-based PM tasks, and that the schizotypal subjects performed worse than the healthy controls and better than the schizophrenic patients.

3.2. Correlation analysis

Correlation analysis between schizotypal traits and cognitive performances in schizotypal participants showed that none of the correlations reached significance,

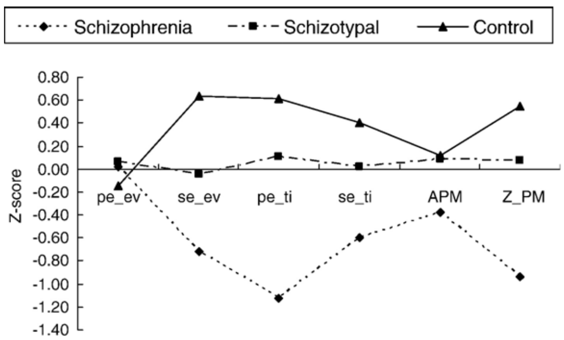

Fig. 2. Prospective memory profiles among groups.

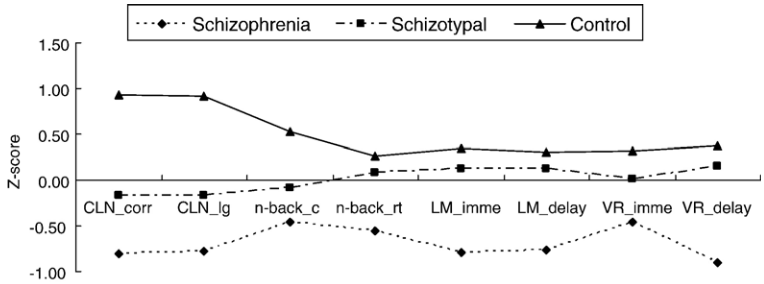

Fig. 3. Other memory profiles among groups.

with r ranging from 0.005 to 0.282 (absolute value), p ranging from 0.974 to 0.074.

Correlations between the clinical variable score and cognitive performance index were calculated for the schizophrenic patients, and none of the correlations reached significance, with p ranging from 0.083 to 0.951. The correlation coefficients between positive symptoms and Z_PM and between duration of illness and n-back correct were −0.46 and −0.42, respectively, and might reach significance if the sample size were increased. When medication side effects (AIMS, BARS) were controlled, the results remained the same.

4. Discussion

In this study, we found that schizophrenic patients showed worse performance in almost all cognitive tasks when compared to healthy controls. Even though some results did not reach significance in a three group comparison, we could see large effect sizes between the schizophrenic and control groups; also, many of the comparisons between psychometrically defined schizotypal subjects and healthy controls demonstrate medium to large effect sizes.

For prospective memory, ongoing task performance was comparative between groups, as it was in Elvevag et al. (2003), which suggests that our task difficulty was reasonable. For PM performance, consistent with the findings of previous studies that schizophrenic patients have PM deficits (Elvevag et al., 2003; Shum et al., 2004; Kumar et al., 2005; Woods et al., 2007), semantic event-based PM, perceptual time-based PM, and semantic time-based PM were all significantly different between groups, and only the difference of perceptual event-based PM and activity-based PM was not significant because the activity-based PM task does not include an interruption of the ongoing task, and there is an external cue that the ongoing task is finished, it is thought to be the easiest of the three types of PM tasks (Kvavilashvili and Ellis, 1996). Hence, it is not surprising that the difference in activity-based PM was not significant between groups. It is generally thought that the time-based PM task is the most difficult type of PM task (Einstein et al., 1992, 1995), and consistent with this view, both the perceptual time-based PM and semantic time-based PM were significantly different between groups. For event-based PM tasks, semantic event-based PM was significant but perceptual event-based PM was not. It is considered that the semantic PM cue requires deeper processing and is more difficult to detect than the perceptual PM cue, so the schizophrenic patients did not have enough cognitive resources to detect the semantic cue when performing the ongoing task. Both Kumar et al. (2005) and Shum et al. (2004) have found that semantic event-based PM is impaired in schizophrenic patients, but to our knowledge, perceptual event-based PM impairment in schizophrenia has not been reported before. In addition, we found that schizotypal subjects showed medium to large effect sizes in semantic event-based PM, perceptual time-based PM, and Z_PM compared to the healthy controls, which indicates that these subjects were also impaired in PM function, but to a lesser degree.

PM performance is affected by working memory (West et al., 2006), and in this study, working memory as measured by the Chinese Letter Number Span was significantly different among groups, so we controlled the total correct score and found that the results remained mainly the same, which suggests that the PM deficit in patients was not caused by a working memory deficit. Thus, prospective memory, especially semantic event-based PM, perceptual time-based PM, and semantic time-based PM, may be a potential endophenotypic marker for schizophrenia, however, study of nonpsychotic relatives of patients with schizophrenia and a follow-up study are needed.

Consistent with the schizophrenic subjects in previous studies (Braff et al., 2007; Cirillo and Seidman, 2003; Joyce, 2005; Conklin et al., 2000, 2005; Lencz et al., 2003; Gur et al., 2007), schizophrenic subjects in this study were impaired in verbal memory and working memory, which suggests verbal memory and working memory deficits in schizophrenic patients. For psychometrically defined schizotypal subjects, most of the literature has focused on attention, which is measured by the Continuous Performance Test (CPT, e.g., Chen et al., 1997; Gooding et al., 2006) and executive function, which is measured by the Wisconsin Card Sorting Test (WCST, e.g., Gooding et al., 1999, 2001; Park et al., 1995; Suhr, 1997; Tallent and Gooding, 1999). The literature on working memory suggests that spatial working memory is impaired in schizotypal individuals (Cohen et al., 2006; Park et al., 1995; Park and McTigue, 1997; Gooding and Tallent, 2003; Tallent and Gooding, 1999), but for verbal memory and auditory working memory, studies have found no significant impairment for schizotypal groups (Lenzenweger and Gold, 2000; Cohen et al., 2006; Jahshan and Sergi, 2007), and the effect sizes are small. The present study found medium to large effect sizes in working memory, but small effect sizes in verbal and visual memory. It was also found that cognitive functions were not correlated with any clinical variables, which may be due to the small sample size, but the results were not inconsistent with those in the literature (Conklin et al., 2005; Kumar et al., 2005).

This study provides a tentative suggestion that prospective memory may serve as a potential endophenotype of schizophrenia. Given the preliminary nature of the present findings, greater evidence of support for all criteria for an endophenotype should be provided for future work. Moreover, there are several limitations of the present study. First, we did not recruit any clinically defined schizotypal cases or collect data on the nonpsychotic relatives of the schizophrenic patients, so we did not know the genetic relatedness of these cognitive functions. Future participant recruitment should extend to these nonpsychotic relatives and clinically defined cases. Second, there were no imaging data, which are more direct for schizophrenic patients when they are performing PM tasks, and would provide more effective evidence to support our hypothesis. Our laboratory, however, is undertaking these studies. Third, the gender ratio in groups was significantly different from group to group, but the gender difference of cognitive functions was not significant so it is unlikely to impact the findings that were obtained.

Notwithstanding these limitations, the present study showed that prospective memory was impaired in schizophrenia spectrum disorders, including individuals with schizotypal personality traits. Future study adopting a more rigorous methodological design and stringent sample inclusion criteria is urged to further examine the stability and heritability of prospective memory in schizophrenia.

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Contributors

Yang Wang and Raymond Chan designed the study, conducted the statistical analyses and wrote the first draft of the manuscript; Xin Yu and Chuan Shi took part in the clinical cases interview and assessment; Jifang Cui and Yongyu Deng took part in the schizotypal cases interview and assessment. All authors contributed and have approved the final manuscript.

Conflict of interest

There are no actual or potential conflicts of interests with respect to the authors' involvement in this manuscript.

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